

This Page Is Inserted by IFW Operations
and is not a part of the Official Record

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

IMAGES ARE BEST AVAILABLE COPY.

**As rescanning documents *will not* correct images,
please do not report the images to the
Image Problem Mailbox.**

(19)



Eur päisches Patentamt
Eur pean Patent Office
Offic uropéen des brev ts

(11)

Publicati n number:

0 077 630
A1

(12)

EUROPEAN PATENT APPLICATION

(21) Application number: 82305413.5

(51) Int. Cl.³: **A 61 K 7/06**

(22) Date of filing: 12.10.82

(30) Priority: 21.10.81 GB 8131752

(43) Date of publication of application:
27.04.83 Bulletin 83/17

(84) Designated Contracting States:
AT BE CH DE FR GB IT LI LU NL SE

(71) Applicant: BEECHAM GROUP PLC
Beecham House Great West Road
Brentford Middlesex(GB)

(72) Inventor: Dixon, Harold
164 Woodland Gardens
Isleworth Middlesex(GB)

(72) Inventor: Day, Pamela Margaret
6 Raymead Way Fetcham
Leatherhead Surrey(GB)

(74) Representative: Cresswell, Thomas Anthony et al,
European Patent Attorney Beecham Pharmaceuticals
Great Burgh Yew Tree Bottom Road
Epsom Surrey KT18 5XQ(GB)

(54) Topical antimicrobial compositions.

(57) A topical antimicrobial composition comprises an aqueous or detergent solution of

- (i) a pyridine thione salt or pyridine thione disulphide
- (ii) a strong chelating agent

and

- (iii) from 0.007 to 1.5% w/w of divalent copper cations.

TOPICAL ANTIMICROBIAL COMPOSITIONS

The present invention relates to topical antimicrobial compositions, such as shampoos, based on pyridine thione as antimicrobial agent.

Zinc pyridine thione (zinc OMADINE*; zinc 2-pyridine thiol-N-oxide, hereinafter referred to as ZPT) is well known as an antimicrobial agent and is frequently included in detergent compositions, especially shampoos for combatting the scalp microorganisms associated with dandruff. Japanese Patent Application No. 50-6171 (laid open no 51-82738 discloses the use of ethylene diamine tetra-acetic acid (EDTA) and alkali metal salts thereof, to improve the adsorption of ZPT onto the hair and scalp.

EDTA has the further effect of solubilising ZPT, thus ZPT/EDTA shampoos are clear whereas shampoos without EDTA consist of a suspension of ZPT particles and are opaque.

Other salts of pyridine thione are known and used as antimicrobial agents. Some of these are, like ZPT, insoluble, but may be solubilised using a strong chelating agent. Others are soluble, particular examples being sodium pyridine thione (NaPT) and pyridine thione disulphide.

* OMADINE is a trade mark of the Olin Corporation.

01

02

03

04

05

06

07

08

09

10

11

12

13

14

15

16

17

18

19

20

21

22

23

24

25

26

27

28

29

30

31

32

33

34

35

36

37

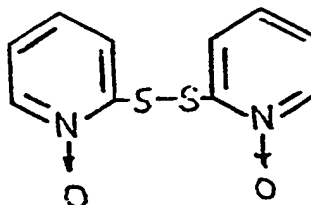
38

It has now surprisingly been found that the anti-microbial effect of dissolved pyridine thione in topical antimicrobial formulations is enhanced by including a strong chelating agent and divalent copper cations in the formulation.

Accordingly the present invention provides a topical antimicrobial composition which comprises an aqueous or detergent solution of

- (i) a pyridinethione salt or pyridine thione disulphide
- (ii) a strong chelating agent
- and (iii) from 0.007 to 1.5% w/v of divalent copper cations.

Pyridine thione disulphide has the formula:



and is commercially available as an adduct with calcium chloride or magnesium sulphate (OMADINE CDS or OMADINE MDS respectively).

An aqueous solution of a pyridine thione salt may be obtained by dissolving a soluble pyridine thione salt, or may be obtained by solubilising an insoluble pyridine thione salt using a strong chelating agent. The chelating agent may be the same as that mentioned under item (ii) above, but it should be understood that a strong chelating agent is essential to the invention even when a soluble pyridine thione salt is employed.

Soluble pyridine thione salts are well known to the skilled person and include for instance sodium pyridine thione. Insoluble pyridine thione salts are also well known, a particular example being ZPT.

Strong chelating agents, suitable for use in the composition of the invention, are well known in the art and are usually di- or polyamines such as ethylene diamine tetra-acetic acid (EDTA), diethylene triamine penta-acetic acid (DTPA), tetraethylene triamine (TET), ethylene diamine (EDA) and diethylene triamine (DETA) or salts thereof. The preferred chelating agent is EDTA or the disodium salt thereof.

It is believed that solutions of pyridine thione undergo chemical changes, especially on exposure to sunlight or artificial light, and that these changes lead to the formation of the active species which is thought to be related to the pyridine thione disulphide. The antimicrobial properties of this material are potentiated by the combination of the strong chelating agent and divalent copper cations.

Compositions according to the present invention may be used to treat a variety of microbial conditions. Thus they may be presented as hair dressings, hair conditioners or hair shampoos for combatting scalp microorganisms such as those associated with dandruff, in particular Pityrosporum ovale. Other presentations of the composition include creams, ointments and lotions for treating scalp microorganisms, superficial mycoses and/or bacterial skin infections.

Suitably, compositions according to the present invention comprise from 0.005 to 5% w/w of pyridine thione excluding the weight of the cation component of the salt. Thus, when ZPT is used the compositions may comprise 0.01 to 2.0% w/w ZPT. When pyridine thione disulphide is used the compositions suitably comprise 0.01 to 2.0% w/w of pyridine thione disulphide excluding the weight of any salt combined in an adduct with the pyridine thione disulphide. Thus when, for instance, OMADINE MDS is employed, the compositions may comprise 0.01 to 2.0% w/w of OMADINE MDS.

Suitably the compositions comprise 0.01 to 5.0% w/w of a strong chelating agent. When an insoluble pyridine thione is employed, a strong chelating agent is also required in equimolar proportions, or in excess, to solubilise the salt. By way of example, from 0.01 to 5.0% w/w EDTA would be used in a composition comprising 0.01 to 2.0 w/w ZPT. If a soluble pyridine thione salt, or pyridine thione disulphide is used, the amount of strong chelating agent required may be reduced, since it is not necessary to solubilise the cation, nevertheless the amount of chelating agent would, suitably, still fall within the above range. The determination of optimum proportions of particular ingredients is, however, within the ability of the skilled person.

Conveniently the copper ions are provided by a simple inorganic copper salt such as copper nitrate or, preferably, copper sulphate. When copper sulphate is used, the above mentioned proportion of copper ions may be achieved using from 0.05 to 1.0% copper sulphate ($\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$).

12 Accessory ingredients such as preservatives,
13 colouring, perfume and conventional excipients in
14 topical formulations may also be included in the
15 compositions described above.

16
17 In a preferred embodiment of the present invention
18 the compositions are presented as hair shampoos and
19 comprise a detergent or mixture of detergents.

20
21 Accordingly the present invention, in a particular
22 aspect, provides a shampoo composition comprising an
23 aqueous or detergent solution of

- 24 (i) a pyridinethione salt or pyridine thione
25 disulphide
26 (ii) a strong chelating agent
27 and (iii) from 0.007 to 1.5% w/w of divalent copper
28 cations.

29
30 Suitably the shampoo comprises from 0.01 to 2% w/w
31 of ZPT and from 0.01 to 5.0% w/w EDTA or an alkali
32 metal salt thereof. Preferably the composition
33 comprises from 0.05 to 1% w/w ZPT, most preferably
34 about 0.2%, and from 0.05 to 5%, most preferably about
 2.5% w/w of EDTA or an alkali metal salt thereof.
 Preferably the disodium salt of EDTA is used.

 Suitably the composition comprises ZPT and copper
 ions in approximately equimolar proportions.

 The most preferred compositions comprise about
 0.2% w/w ZPT, about 2.5% w/w EDTA disodium salt and
 about 0.15% w/w copper sulphate.

1
2 The shampoo compositions described above may
3 include any conventional detergent. Selection of such
4 detergents is a matter of common general knowledge.
5 For shampoo compositions it is usual to use an anionic
6 detergent, for example alkali metal, ammonium or
7 hydroxyalkylamine salts of alkyl sulphates, alkyl
8 benzene sulphonates, alkyl sulphones, α -alkenyl-
9 sulphonates, polyoxyethylenealkyl sulphonates and
10 polyoxyethylenealkylphenyl sulphates. Suitable shampoo
11 detergents therefore include sodium lauryl ether
12 sulphate. Mixtures of detergents may also be used.

13
14 Shampoo compositions usually contain from 10 to
15 90% w/w of detergent or detergent mixture. More
16 suitable the compositions contain from 10 to 16% w/w.

17
18 The shampoo compositions of the invention may also
19 contain various conventional accessory ingredients
20 including perfume, colouring, preservatives, foam
21 builders, conditioning agents, materials to render the
22 composition opaque, pearlescent or opalescent, and/or
23 agents to adjust or maintain the pH of the composition.

24
25 Compositions of the invention may also be
26 presented as hair dressings and lotions, ointments and
27 creams. In each case the formulation comprises a
28 pyridine thione salt or disulphide, a strong chelating
29 agent and divalent copper cations dispersed in a
30 conventional carrier. Typical carrier formulations are
31 described in the literature - for instance in Harry's
32 Cosmeticology 6th Edition, Leonard Hill Books, London
33 (1973).
34

7 The compositions of the present invention may be
8 produced by admixing the various constituents.
9 When an insoluble pyridine thione salt is used as
10 antimicrobial agent the salt and the strong chelating
11 agent are admixed with the carrier and the mixture is
12 allowed to clear and stand in the light for a period of
13 days of weeks. Alternatively, the mixture may be
14 exposed to artificial ultra violet light to hasten the
15 process. The copper ions, in the form of a copper
16 salt, are then admixed with the composition. When a
17 soluble pyridine thione salt, or pyridine thione
18 disulphide is used exposure to light is not necessary
19 and the composition can be prepared simply by admixing
20 the pyridine thione salt or pyridine thione disulphide
21 with the carrier and adding divalent copper ions.

22 Various accessory ingredients may be added
23 subsequently or at any convenient stage during this
24 process.

25 It will be appreciated that, during the production
26 of the composition, various chemical changes occur.
27 Thus insoluble pyridine thione salts are solubilised by
28 chelation of the metal cation and, it is believed, the
29 pyridine thione moieties react together in light to
30 form the antimicrobially active species.

31 Accordingly, the present invention provides a
32 process for producing a composition as hereinbefore
33 described which process comprises dissolving or
34 solubilising a pyridine thione salt or pyridine thione
35 disulphide and a strong chelating agent and admixing
copper ions with the product.

2 When an insoluble pyridine thione salt is used the
3 process suitably comprises the further step of exposing
4 the mixture to ultra violet light prior to adding the
5 copper ions.

6 The present invention also provides a method for
7 treating microorganism infections of the skin,
8 particularly dandruff, superficial mycoses and
9 bacterial skin infections, which method comprises
0 applying an effective, non-toxic, amount of a
1 composition as hereinbefore defined, to the human skin.
2

3 The present invention will now be illustrated by
4 the following Examples and Biological Data, which are
5 not intended to limit the scope of invention in any
6 way.
7

8 As used herein the term "SLES detergent solution"
9 refers to a 27.5% w/v aqueous solution of sodium lauryl
0 ether sulphate.
1

2 The following abbreviations have been employed in
3 the Examples:-
4

5 Zinc pyridine thione	ZPT
6 Pyridine thione disulphide magnesium	
7 sulphate adduct	MDS
8 Ethylene diamine tetraacetic acid	EDTA

9 Proportions of ingredients are proportions by
0 weight unless otherwise specified.
1

2 Compositions described in the Examples may be
3 produced by conventional techniques.
4
5
6

EXAMPLE 1

A detergent composition suitable for use as an antidandruff shampoo is formulated as follows:

	% by weight
SLES detergent solution	60
Coconut diethanolamide	4
EDTA disodium salt	2.5
ZPT	0.2
Copper sulphate	0.15
U 834 Blue No 1	0.01
Preservative	0.01
Distilled water	to 100

Sodium lauryl ether sulphate, coconut diethanolamide, water, EDTA disodium salt and ZPT are admixed and allowed to clear. The clear solution is left to stand in light at room temperature for 7 to 14 days, after which period the copper sulphate, colour and preservative are added.

The formulation remained as a clear blue liquid and retained full antimicrobial activity when stored at room temperature in sealed containers for 12 months.

01

02

EXAMPLE 2

03

04 A water-in-oil antimicrobial composition may be
05 prepared from the following ingredients:-

06		
07	ZPT or MDS	0.02%
08	EDTA (Di-Sodium Salt)	0.25%
09	Copper Sulphate	0.015%
10	Mineral Oil	18.0%
11	Beeswax	3.0%
12	Ethoxylated Lanolin	5.0%
13	Borax	0.5%
14	Magnesium Sulphate	0.1%
15	Perfume	qs
16	Water to	100%

17

18

EXAMPLE 3

19

20 An oil-in-water composition may be prepared from
21 the following ingredients:-

22		
23		
24	ZPT or MDS	0.02%
25	EDTA (Di-Sodium Salt)	0.25%
26	Copper Sulphate	0.015%
27	Stearic Acid	3.0%
28	Propylene Glycol Mono Stearate	1.0%
29	Mineral Oil	4.0%
30	Glycerin	2.5%
31	Sodium Carboxymethyl Cellulose	0.3%
32	Triethanolamine	1.0%
33	Perfume	qs
34	Water to	100%

35

36

EXAMPLE 4

An antimicrobial composition may be prepared from the following ingredients:-

ZPT or MDS	0.02%
EDTA (Di-Sodium Salt)	0.25%
Copper Sulphate	0.015%
Stearic Acid	3.0%
Propylene Glycol Mono Stearate	1.0%
Polawax	0.5%
Mineral Oil	4.0%
Glycerin	2.5%
Carbopol 934	0.5%
Triethanolamine	1.0%
Perfume	qs
Water to	100%

EXAMPLE 5

A mild astringent skin lotion may be prepared from the following ingredients:-

ZPT or MDS	0.02%
EDTA (Di-Sodium Salt)	0.25%
Copper Sulphate	0.015%
Glycerine	5.0%
Rose Water	15.0%
Alcohol (95%)	30.0%
Menthol	0.2%
Water to	100%

01

02

EXAMPLE 6

03

04

An antidandruff hair conditioner may be prepared
from the following ingredients:-

05

06

07

08

09

10

11

12

13

14

15

16

17

ZPT or MDS

EDTA (Di-Sodium Salt)

Copper Sulphate

Stearyl Alcohol

Cetyl Alcohol

Glycerol Monostearate

Alcohol (Perfumery Quality)

Perfume

Water to

0.02%

0.25%

0.015%

1.0%

2.0%

1.0%

45.0%

qs

100%

BIOLOGICAL DATA

I The activity of various detergent and shampoo formulations, diluted 10 fold, against Pityrosporum ovale (NCTC 3074) was assayed using the disc diffusion method. P. ovale was grown on agar plates and incubated at 37°C. Zones of inhibition were measured after 48 hours. Results are given in Table I as an average of 5 replicates with the effect of a similar formulation containing only 1% w/w ZPT as a comparison.

i) Detergent Formulation:

	<u>% by weight</u>
SLES detergent solution	60
ZPT	0.2
EDTA disodium salt	2.5
Copper sulphate ($\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$, Analar)	See table 1
Distilled water	to 100
pH unadjusted, approx 5.0	

ii) Shampoo Formulations:

	<u>% by weight</u>
SLES detergent solution	60
Coconut diethanolamide	4.0
ZPT	0.2
EDTA disodium salt	2.5
Copper sulphate ($\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$, Analar)	See table 1
2-Bromo-2-nitropropane-1,3-diol (Bronopol)	0.01
U 834 Blue No 1	0.001
Distilled water	to 100
pH unadjusted, approx 5.0	

- 14-

TABLE 1Mean zone of inhibition (mm)

CuSO ₄ ·5H ₂ O % by weight	Formulation	
	Detergent	Shampoo
0.0	5.08 ± 0.54	5.7 ± 1.5
0.05	9.13 ± 0.88	*
0.1	10.75 ± 0.58	11.14 ± 0.65
0.15	10.2 ± 0.67	12.24 ± 0.72
0.2	10.27 ± 1.05	12.58 ± 0.76
0.25	11.38 ± 0.56	11.68 ± 0.8
0.3	*	11.52 ± 0.56
1% ZPT	6.74 ± 0.42	6.77 ± 0.76

* Not tested

- 15 -

II The fungicidal activity of detergent formulations was assayed by contacting P. ovale (NCTC 3074) with the formulation for one hour followed by washing and membrane filtration. The colonies of P. ovale were then scored and counted. Results are given in Table II with control formulations for comparison.

<u>Detergent Formulation</u>	<u>% by weight</u>			
	Formulation 1	2	3	4
SLES detergent solution	60	60	60	60
ZPT	0.0	0.0	0.2	0.2
EDTA disodium salt	0.0	0.0	2.5	2.5
Copper sulphate ($\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$)	0.0	0.3	0.0	0.3
Distilled water	to 100	100	100	100

- 16 -

TABLE IIFungicidal Effect

Formulation	$\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$ (% by weight)	Score after one hour	% kill
1	0.0	6	TNTC
2	0.3	5	TNTC
3	0.0	5	TNTC
4	0.3	3½	ca 50

TNTC : too numerous to count

Scoring:

- 3½ Colonies too numerous to count but well spaced
- 5 Heavy growth but not entirely confluent
- 6 Heavy confluent growth

- 17 -

III In vitro activity of various commercial anti-dandruff shampoo formulations was compared with the ZPT/EDTA/Copper combination evaluated in the P. ovale test system described above. Results are given in Table III.

TABLE III

*Shampoo	Active Ingredient	Zone of Inhibition (mm)
A	0.2% ZPT/EDTA/Cu	10.3 ± 0.6
B	1% ZPT	5.3 ± 0.69
C	2.5 Selenium Disulphide	7.4 ± 0.42
D	Coal Tar Extracts	< 1
E	Triclosan	< 1

* Diluted 1:10 for testing

CLAIMS

1. A topical antimicrobial composition which comprises an aqueous or detergent solution of
 - (i) a pyridine thione salt or pyridine thione disulphide
 - (ii) a strong chelating agent
 - and (iii) from 0.007 to 1.5% w/w of divalent copper cations
2. A composition as claimed in claim 1 comprising from 0.005 to 5% w/w of a pyridine thione salt excluding the weight of the cation component of the salt.
3. A composition as claimed in claim 1 or claim 2 comprising from 0.01 to 2.0% w/w of zinc pyridine thione.
4. A composition as claimed in claim 1 comprising from 0.01 to 2.0% w/w of pyridine thione disulphide.
5. A composition as claimed in any one of claims 1 to 4 comprising from 0.01 to 5.0% w/w of a strong chelating agent.
6. A composition as claimed in any one of claims 1 to 5 wherein the chelating agent is selected from ethylene diamine tetra-acetic acid, diethylene triamine penta-acetic acid, tetraethylene triamine, ethylene diamine, diethylene triamine and salts thereof.
7. A composition as claimed in any one of claims 1 to 6 comprising from 0.05 to 1.0% copper sulphate.

8. A composition as claimed in any one of claims 1 to 7 presented as a shampoo and comprising from 0.01 to 2% w/w zinc pyridine thione disulphide, from 0.01 to 5.0% w/w ethylene diamine tetra-acetic acid or an alkali metal salt thereof, from 0.05 to 1.0% w/w copper sulphate and 10 to 90% w/w of detergent or detergent mixture.
9. A process for producing a composition as defined in claim 1 which process comprises dissolving or solubilising a pyridine thione salt or pyridine thione disulphide and a strong chelating agent and admixing divalent copper cations with the product.
10. A process as claimed in claim 9 comprising the additional step of exposing the dissolved or solubilised pyridine thione salt or pyridine thione disulphide and strong chelating agent to ultra violet light prior to the addition of the copper ions.



DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl. 3)
X,Y	--- US-A-3 940 482 (PAUL SHELDON GRAND) * column 3, lines 1-5, 23-30 *	1-10	A 61 K 7/06
Y	--- GB-A- 807 787 (FREDERICK VICTOR WELLS) * page 1, lines 62-67; page 2, lines 86-111; claims 1-4 * -----	1-10	
			TECHNICAL FIELDS SEARCHED (Int. Cl. 3)
			A 61 K
The present search report has been drawn up for all claims			
Place of search THE HAGUE		Date of completion of the search 19-01-1983	Examiner BRINKMANN C.
CATEGORY OF CITED DOCUMENTS			
X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document		T : theory or principle underlying the invention E : earlier patent document, but published after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document	